EVOLUTION OF HEMODYNAMICS AFTER ORTHOTOPIC HEART AND HEART-LUNG TRANSPLANTATION: EARLY RESTRICTIVE PATTERNS PERSISTING IN OCCULT FASHION

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Evolution of Hemodynamics After Orthotopic Heart and Heart-Lung Transplantation: Early Restrictive Patterns Persisting in Occult Fashion

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Though successfully transplanted hearts respond in such a way that individuals remain remarkably asymptomatic, they do not function normally. Characterization of early hemodynamic patterns and their evolvement has not been done. The evolution of hemodynamic indices in 20 patients receiving orthotopic heart (n = 17) or combined heart-lung (n = 3) transplants is therefore documented. In 15 isolated heart recipients, right heart catheterization was performed at 24 to 48 hours, 1 to 2 weeks, 4 to 8 weeks, and greater than 3 months after surgery at the time of routine endomyocardial biopsy. Early, patients had elevated mean blood pressure (96 ± 14 mm Hg, mean ± standard deviation), mean right atrial pressure (15 ± 6 mm Hg), right ventricular end-diastolic pressure (16 ± 7 mm Hg), mean pulmonary artery pressure (30 ± 7 mm Hg), and mean pulmonary capillary wedge pressure (19 ± 6 mm Hg), but normal resting heart rate (96 ± 14 beats/min) and cardiac output (5.6 ± 1.6 L/min). Heart rate, blood pressure, and output did not change during follow-up, but right atrial pressure decreased dramatically (4 ± 2 mm Hg at 3 months), as did right ventricular end-diastolic pressure (4 ± 4 mm Hg), mean pulmonary artery pressure (21 ± 8 mm Hg), and pulmonary capillary wedge pressure (11 ± 4 mm Hg). Analysis of right heart filling dynamics revealed an abnormal inspiratory rise in mean right atrial pressure (15 ± 6 and 27 ± 7 mm Hg at 24 to 48 hours) that subsequently resolved. In eight patients whose resting follow-up right heart pressures normalized, rapid volume challenge uncovered occult restrictive right atrial pressure patterns that increased from 4 ± 4 to 9 ± 4 mm Hg after infusion of saline solution. Kussmaul's response was not apparent with prevolume infusion, but volume expansion caused appearance of this hemodynamic pattern. All patients had early evidence of tricuspid insufficiency, but in two patients, the Doppler regurgitant fraction was over 50%. These two individuals had hemodynamics similar to the other 15 patients initially, but in contrast, their right heart filling pressures did not change during follow-up. Other significant echocardiographic findings included enlarged atria and increased left ventricular mass in all patients. In two of three combined heart-lung transplant patients, similar hemodynamic patterns were evident. Rejection indices did not correlate with hemodynamic observations. Thus a characteristic evolvement of hemodynamics in heart and heart-lung transplants that mimic dynamics associated with restrictive myocardial disease is documented. These findings generally resolve, may not be related to rejection severity or fibrotic infiltrates, and require volume infusion to uncover an occult process. J HEART TRANSPLANT 1987;6:34-43.

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Heart transplantation is now an accepted therapeutic option and the only ministration that significantly alters the natural history of end stage heart disease. Though successfully transplanted hearts respond in such a way that individuals remain remarkably asymptomatic,[1,2] they do not function normally. Clinical and experimental studies have demonstrated that orthotopic heart transplants are denervated organs with increased mass.[3,4] Additionally, these preparations are subject to interstitial infiltrative processes associated with rejection,[5] and it has also been suggested that chronic cyclosporine therapy creates a unique interstitial fibrosis.[5-7]

Still, there have only been a few reports characterizing hemodynamic indices in heart transplant patients since the procedure was first performed in 1967.[8-15] Most of these reports describe long-term hemodynamic patterns postoperatively and do not detail hemodynamic observations early in the postoperative period or address the evolution of the orthotopically transplanted heart's dynamics. Recently, a few case series summarizing hemodynamic characteristics at the 1- or 2-year follow-up point in cyclosporine-treated patients have appeared.[16,17]

We have observed a unique and characteristic progression of dynamic patterns in transplant patients since our program was reinstituted in February 1984. Because no longitudinal studies defining these abnormalities have been performed and successful postoperative management requires an understanding of these parameters, we prospectively evaluated hemodynamic indices and describe them herein.

METHODS

Patients

In a 22-month period, 20 orthotopic heart (n = 17) and combined heart-lung (n = 3) transplant procedures were performed at The Multi-Organ Transplantation Center of The Methodist Hospital and Baylor College of Medicine. The patients' age range was 12 to 57 years (mean, 38 years), and the cause of end stage heart disease in heart transplantation patients was ischemia in 10, idiopathic dilated myopathy in six, and valvular heart disease with myocarditis in one patient. Heart-lung transplantation was performed for end stage alpha-1 antitrypsin deficiency, bronchiolitis obliterans, and idiopathic pulmonary fibrosis once each. The hemodynamics of heart-lung transplantation were evaluated separately, as were two heart transplant patients with significant postoperative tricuspid insufficiency.

Patient Follow-up

For the heart transplant patients, right heart catheterization—after routine diagnostic right ventricular endomyocardial biopsy—was performed postoperatively at 24 to 48 hours in 15 patients, between 1 and 2 weeks in 13 patients, between 2 and 4 weeks in 14 patients, between 4 and 8 weeks in 11 patients, and after 3 months in seven patients. Data are presented separately for the three heart-lung transplantation patients at 48 hours, 1 week, and 2 weeks.

Operative Technique

We use standard operative techniques for performing orthotopic heart and heart-lung transplantation.[8,10,14,18] On-site donor harvesting was performed for eight heart and all three heart-lung transplant patients. Distal-site procurement with hypothermic cardioplegic arrest provided hearts for nine patients. Total cardiac ischemic time for locally procured organs was 62 minutes (range, 45 to 89 minutes) and for organs obtained distally, 262 minutes (range, 176 to 331 minutes).

Postoperative Care

Postoperatively, all patients received cyclosporine, 7 to 10 mg/kg/day, in two divided dosages. Dosage adjustments were made to keep whole blood radioimmuno-

TABLE I Heart transplant hemodynamics: characteristics during follow-up (measured indices*)

Parameter	Follow-up after transplantation				
	24-48 hr (n† = 15)	1-2 wk (n = 13)	2-4 wk (n = 12)	4-8 wk (n = 11)	>3 mo (n = 7)
Heart rate (beats/min)	96 ± 14	90 ± 19	99 ± 15	96 ± 12	97 ± 7
Mean blood pressure‡	102 ± 16	101 ± 14	101 ± 15	103 ± 12	107 ± 15
Mean pulmonary artery pressure	30 ± 7	27 ± 8	23 ± 9§	16 ± 6§	21 ± 8§
Mean pulmonary capillary wedge pressure	19 ± 6	18 ± 7	15 ± 8	12 ± 5§	11 ± 4§
Cardiac output (L/min)	5.6 ± 1.6	6.1 ± 1.0	5.7 ± 1.0	5.3 ± .8	5.6 ± 1.4
Mean right atrial pressure	15 ± 6	12 ± 8	7 ± 5§	5 ± 5§	4 ± 2§
Right ventricular end-diastolic pressure	16 ± 7	12 ± 7	8 ± 6§	4 ± 5§	4 ± 4§

*Mean ± standard deviation for group.
†Number of patients studied.
‡All pressure measurements are mm Hg.
§ $p < 0.05$ compared with initial study.

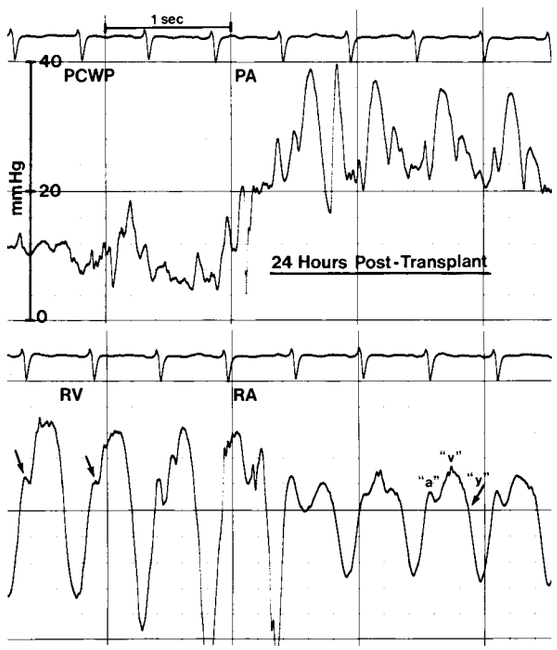

FIGURE 1 Typical pressure tracing 24 hours after orthotopic heart transplantation, demonstrating typical right heart hemodynamic abnormalities seen in early recovery period. *Arrow* points to right ventricular end-diastolic pressure. *PCWP,* Pulmonary capillary wedge pressure; *PA,* pulmonary artery pressure; *RV,* right ventricular pressure; *RA,* right atrial pressure; *"a",* right atrial A wave; *"v",* right atrial V wave; *"y",* right atrial Y descent.

assay levels 700 to 1000 ng/ml, the blood urea nitrogen level less than 40, serum creatinine clearance less than 2.0, and total bilirubin level under 2.0 mg/dl. Patients received catecholamine support for the first 72 hours after surgery, and this included dopamine, 1 to 4 μg/kg/min, and epinephrine, 0.01 μg/kg/min. Right ventricular endomyocardial biopsy and right heart catheterization were performed at the times indicated with standard techniques.[5,19]

Data Acquisition

After obtaining informed consent and right ventricular endomyocardial biopsy, right heart catheterization was performed with a triple-lumen, balloon-tipped, flow-directed thermodilution catheter in a standard fashion. The mean right atrial, right atrial A and V waves, right atrial Y descent, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures were measured at end expiration and during inspiration off mechanical ventilators and were permanently recorded with a strip chart system. Mean pressures were determined by electronic integration, and cardiac output was obtained in quintuplicate by a thermodilution computer with variation of less than 10%. Arterial pressure was measured with a mercury manometer and cuff over the brachial artery. Calculated hemodynamic indices were obtained with the use of appropriate formulas and included cardiac index, stroke volume, stroke work, systemic vascular, total pulmonary, and pulmonary arteriolar resistances.

In eight patients who had developed normal resting end-expiration right heart hemodynamics during follow-up (mean, 4 months; range, 1 to 17 months), acute volume loading was performed by infusing 500 ml of normal saline solution within 2 minutes into a large central vein. The same hemodynamic indices were obtained before and immediately after this volume challenge.

Echocardiographic evaluation was performed on the day of catheterization with a two-dimensional system equipped with cardiac Doppler ultrasound capabilities. Valvular regurgitation, ventricular function, and left ventricular mass and volume were evaluated with our previously reported methods.[20,21]

Endomyocardial biopsies were stained with hematoxylin and eosin as well as trichrome and reviewed by our pathologist for rejection and fibrosis.[5,19] Rejection was graded 0 to 4, according to standard criteria, and fibrosis was qualitatively assessed as being present and significant or absent.[5,19]

Data Analysis

Data were stored and analyzed with the data management systems of the CLINFO Project (Division of Research Resources, National Institutes of Health, Bethesda, Md.). Statistical analysis, comparing hemodynamic changes, was performed with analysis of variance (ANOVA) and the nonparametric paired-value Wilcoxon signed-rank test. Paired *t* test was used to compare before and after volume loading states. Statistical significance was deemed present if the *p* value was less than 0.05.

RESULTS

Table I summarizes measured hemodynamic indices observed in the period after transplant in the 15 patients undergoing orthotopic heart transplantation who did not have significant postoperative tricuspid insufficiency. As can be seen, patients had normal resting heart rate and cardiac output. Mean pulmonary artery pressure and blood pressure were elevated as were mean right atrial, pulmonary capillary wedge, and right ventricular end-diastolic pressures. Of significance is that the heart rate, mean blood pressure, and cardiac output did not change during longitudinal follow-up. Interestingly, the mean right atrial pressure decreased significantly during the 3-month period of follow-up, as did the right ventricular end-diastolic pressure. This was associated with concomitant decrement in pulmonary capillary wedge pressure and mean pulmonary artery pressure. Figure 1 demonstrates typical pressure tracings 24 hours after orthotopic heart transplantation. There is mild pulmonary hypertension with a normal pulmonary capillary wedge pressure and an 8 to 10 mm Hg pulmonary artery diastolic to pulmonary capillary wedge pressure gradient. The right ventricular end-diastolic and right atrial pressure tracings are markedly abnormal with extremely high pressures (end-diastolic pressure of 24 mm Hg and right atrial V wave pressure of 26 mm Hg). There is marked accentuation of the right atrial Y descent.

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TABLE II Heart transplant hemodynamics: right heart filling dynamics during follow-up

Parameter	Follow-up after transplantation				
	24-48 hr (n* = 15)	1-2 wk (n = 13)	2-4 wk (n = 12)	4-8 wk (n = 11)	>3 mo (n = 7)
Mean right atrial pressure†					
End expiration	15 ± 6	12 ± 8	7 ± 5‡	5 ± 5‡	4 ± 2‡
Inspiration	17 ± 7	10 ± 7‡	6 ± 7‡	4 ± 6‡	4 ± 4‡
Right atrial A wave					
End expiration	17 ± 7	12 ± 8	10 ± 7‡	6 ± 4‡	5 ± 3‡
Inspiration	18 ± 7	12 ± 7‡	10 ± 7‡	5 ± 5‡	5 ± 5‡
Right atrial V wave					
End expiration	18 ± 7	13 ± 8	10 ± 6‡	7 ± 4‡	7 ± 3‡
Inspiration	20 ± 7	13 ± 7‡	11 ± 7‡	7 ± 6‡	8 ± 5‡
Right atrial Y descent§					
End expiration	8 ± 3	5 ± 2	6 ± 3	5 ± 2‡	6 ± 1‡
Inspiration	13 ± 4	12 ± 6	12 ± 5	8 ± 3	12 ± 3
Right ventricular end-diastolic pressure					
End expiration	16 ± 6	12 ± 7	9 ± 6‡	6 ± 4‡	4 ± 3‡
Inspiration	16 ± 7	12 ± 7	8 ± 6‡	4 ± 5‡	4 ± 4‡

*Number of patients studied.
†All pressure measurements are mm Hg.
‡ $p < 0.05$ compared with initial study.
§Absolute quantity of descent (peak of V wave to nadir before A wave).

Derived hemodynamic indices (initial 24 to 48 hours measurement in parentheses) demonstrated no significant change in cardiac index (2.9 ± 0.8 L/min/m²), stroke volume index (31 ± 9 ml/beat/m²), stroke work index (34 ± 13 gm-m/m²), systemic vascular resistance (1316 ± 426 dynes·sec·cm⁻⁵), or pulmonary vascular resistance (184 ± 140 dynes·sec·cm⁻⁵) during the follow-up period.

Table II delineates right heart filling dynamics during long-term follow-up. As mentioned, mean right atrial pressure decreases during the follow-up period. Interestingly, in the early follow-up period (48 hours), there is a paradoxical rise in mean right atrial pressure with inspiration. This rise is contributed to mostly by the right atrial V wave, which increases from 18 to 20 mm Hg with a concomitant augmentation of right atrial Y descent. All right heart filling dynamics at end expiration approach a baseline that might be considered within normal ranges by the 4- to 8-week follow-up period. However, subtle abnormalities remain and are characterized by excessive augmentation of inspiratory right atrial Y descent and lack of a significant decrease in mean right atrial pressure during inspiration. Figure 2 demonstrates normal right heart hemodynamics 1 year after heart transplantation. Only after volume loading can right atrial and right ventricular filling abnormalities be seen.

Volume loading was performed in eight patients after mean resting end-expiratory right atrial pressure had normalized during follow-up. In these patients, a dramatic and significant rise in baseline right heart filling pressures was apparent (Figure 3). Mean right atrial pressure rose from 4 ± 4 to 9 ± 4 mm Hg ($p = 0.002$), with concomitant increases in right atrial A and V valves and right ventricular end-diastolic pressure (Table III). Additionally, there was a dramatic rise in amplitude of the right atrial Y descent. Importantly, despite the inspiratory decrease in mean right atrial pressure before volume loading, afterward there was an opposite trend with mean right atrial pressure signifi-

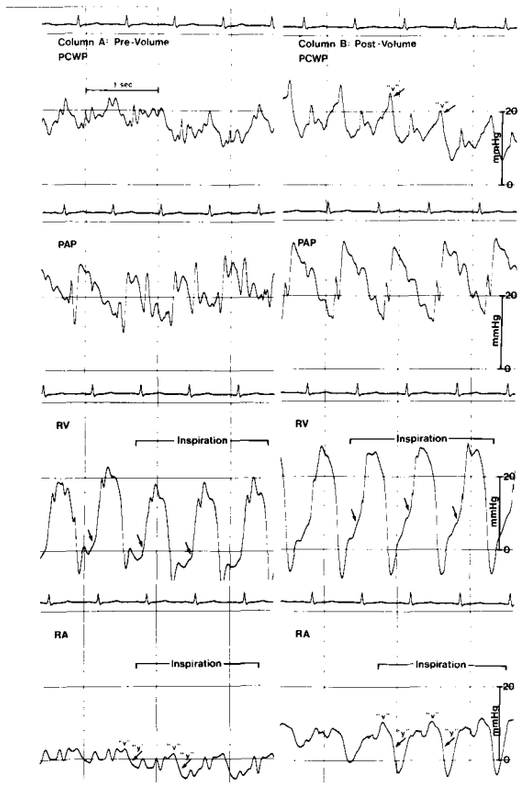

FIGURE 2 Typical pressure tracing 1 year after orthotopic heart transplantation. Column A is before volume loading and demonstrates normal resting hemodynamic patterns. Column B is after infusion of 500 ml normal saline solution into central vein within 2 minutes and demonstrates accentuation of V wave on pulmonary capillary wedge tracing *(PCWP),* increased pulmonary artery pressure *(PAP),* inspiratory increase in right ventricular *(RV)* end-diastolic pressure *(arrows),* and dramatic right atrial pressure wave pattern changes. *"v"*, right atrial *(RA)* or PCWP V wave; *"y"*, right atrial Y descent.

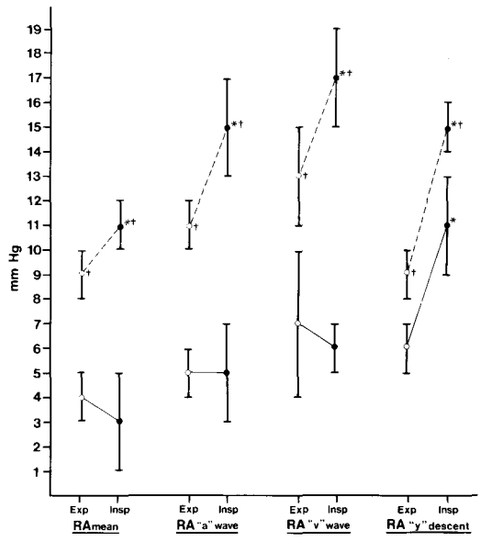

FIGURE 3 Effect of volume loading in eight patients on right heart filling dynamics. Group means (±standard error of the mean) are presented before *(solid lines)* and after administration of 500 ml normal saline solution *(dashed lines). Open circles,* End-expiratory pressure; *closed circles,* peak inspiration; *asterisks, p* <0.05 inspiratory pressure vs end expiration; *daggers, p* <0.05 after vs before volume infusion.

cantly increasing during respiration (Figure 4). Similar findings were noted with the right atrial A wave, right atrial V wave, and right ventricular end-diastolic pressure. This paradoxical rise in right heart filling pressures occurring with inspiration is analogous to Kussmaul's sign seen in patients with restricted filling of the right heart.

Other changes that occurred with volume loading (Table III) were an increase in mean pulmonary artery pressure (19 ± 8 to 23 ± 8 mm Hg; $p = 0.004$) and an increase in mean pulmonary capillary wedge pressure (11 ± 8 to 15 ± 7 mm Hg; $p < 0.001$). Heart rate, mean blood pressure, cardiac output, and stroke volume index, as well as systemic vascular and pulmonary vascular resistance, did not change significantly.

There were no substantive differences in hemodynamic indices between patients receiving organs harvested distantly or locally, and no correlation existed between total ischemic time and right heart filling dynamics.

HEART-LUNG TRANSPLANT HEMODYNAMICS

The hemodynamics of combined heart-lung transplant patients are similar to isolated heart transplants. Mean right atrial pressure was 13 ± 8 mm Hg, mean right ventricular end-diastolic pressure was 13 ± 8 mm Hg, mean pulmonary artery pressure equaled 23 ± 6 mm Hg, and mean blood pressure was 96 ± 9 mm Hg. Right heart filling dynamics in two of three patients were virtually identical to the orthotopic heart transplant patients. One patient had normal right heart pressures from the earliest postoperative period. The two patients first mentioned also had elevated pulmonary vascular resistance (429 and 683 dynes·sec·cm^{-5}), despite the insertion of normal lungs, but this seemed to

TABLE III Transplant hemodynamics: effect of volume loading* (n† = 8)

Parameter	Baseline	Volume load	*p*
Heart rate (beats/min)	103 ± 13‡	100 ± 11	NS§
Mean blood pressure ||	112 ± 13	96 ± 36	NS
Mean pulmonary artery pressure	19 ± 8	23 ± 8	0.004
Mean pulmonary capillary wedge pressure	11 ± 8	15 ± 7	<0.001
Cardiac output	5.37 ± 1.0	5.73 ± 1.35	NS
Mean right atrial (RA) end expiration	4 ± 4	9 ± 4	0.002
Mean RA inspiration	3 ± 5	11 ± 4	0.002
RA A wave	5 ± 4	11 ± 4	0.001
RA A inspiration	5 ± 5	15 ± 6	<0.001
RA V wave end expiration	6 ± 5	13 ± 5	<0.001
RA V inspiration	7 ± 7	17 ± 6	0.002
RA Y descent	6 ± 2	9 ± 3	<0.001
RA Y inspiration	11 ± 5	15 ± 4	0.01
Right ventricular end-diastolic pressure (RVEDP)	4 ± 2	9 ± 4	0.006
RVEDP inspiration	4 ± 5	11 ± 6	<0.001

*Mean follow-up when volume loading was performed (4 months; range, 1.25 to 16.75 months).
†Number of patients studied.
‡Mean ± standard deviation.
§Not significant is >0.05.
||All pressure measurements are mm Hg.

be the result of elevated left heart filling pressures. Volume challenge has not been performed in this group.

ECHOCARDIOGRAPHIC EVALUATION

All patients had echocardiographically enlarged right and left atria detected 48 hours after surgery. Mean right atrial dimension was 5.2 ± 1.0 cm (range, 4.8 to 6.1), and left atrial size was 5.3 ± 1.2 cm (range, 4.6 to 6.2). These dimensions did not change significantly during longitudinal follow-up. One patient had tricuspid valve prolapse, but no other valvular abnormalities were noted. Left and right ventricular dimensions were normal, and the mean left ventricular ejection fraction was 62% ± 10%. As a group, this index of systolic function did not change significantly. However, one isolated heart transplant patient developed severe rejection (grade 4) at the 2- to 4-week point with a decline in ejection fraction from 57% to 40%. At the 3-month catheterization date, it was 37% despite resolution of rejection. Left ventricular mass was increased in all patients at the 2- to 4-week observation point, manifest by an increase in left ventricular posterior and interventricular septal wall diastolic thickness (mean, 1.3 ± 0.05 cm; range, 1.2 to 1.6).

Pulsed Doppler echocardiographic evaluation demonstrated mild to moderate tricuspid regurgitation in all patients. The majority of patients had mild regurgitation, but the Doppler calculated regurgitant fraction was greater than 50% in two patients, and this was apparent at the initial study, with significant regurgitation persisting throughout the follow-up period. Both patients were critically ill at the time of transplant with mean pulmonary artery pressures of 55 and 50 mm Hg.

After transplant, the patients with severe tricuspid insufficiency had elevated right heart filling pressures (20 and 27 mm Hg) and markedly elevated pulmonary resistances (376 and 673 mm Hg) that, like the heart-lung transplant patients, seemed primarily caused by elevated left heart filling pressures. The tricuspid regurgitation was noted to decrease slightly as pulmonary resistance dropped, but unlike other patients, these two did not have hemodynamics that normalized during longitudinal follow-up.

Pericardial effusions were not a significant problem. Small effusions were noted in seven patients at 48 hours, but these rapidly dissipated and were never large enough to account for significant hemodynamic derangement.

PATHOLOGIC FINDINGS

All hemodynamic measurements were done after first obtaining right ventricular endomyocardial biopsy. The mean rejection score was 1.5 ± 0.5 (range, 0 to 3) at 24 to 48 hours; 2.0 ± 1 (range 1 to 3) at 1 to 2 weeks; 2.5 ± 2 (range, 2 to 4) at 4 to 8 weeks; and 1.5 ± 0.5 (range, 0 to 3) at >3 months. Only one patient had grade 4 rejection. This appeared at the 2- to 4-week

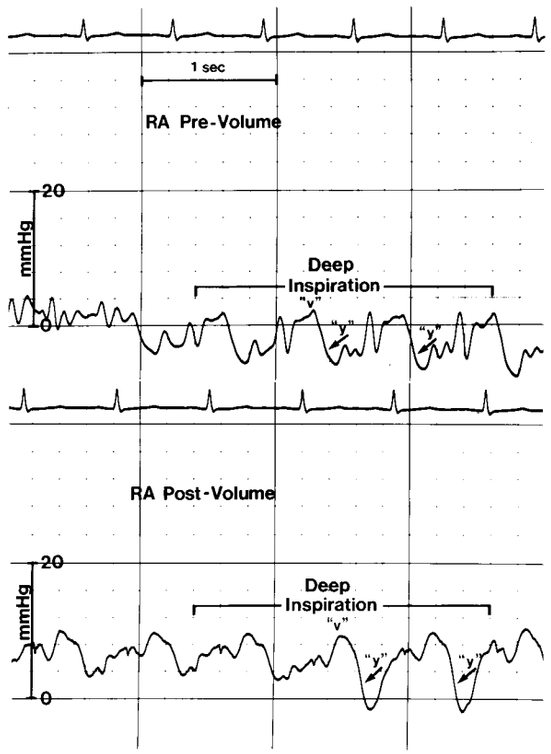

FIGURE 4 Typical changes noted in right atrial *(RA)* pressure tracing after volume loading when resting hemodynamics have returned to normal during longitudinal follow-up. After saline solution infusion, expiratory pressure increases, and there is loss of normal inspiratory decline in pressure with augmentation of V wave and Y descent.

interval and persisted through the 4- to 8-week window and was grade 2 at the 3-month follow-up point.

Only one patient had significant fibrosis, and this was seen in conjunction with the episode of severe rejection. One patient died of fulminant rejection 8 days after heart transplantation, before his second hemodynamic assessment. Initially (48 hours), he had only mild rejection (grade 2).

DISCUSSION

We have documented a characteristic evolution of hemodynamic patterns in patients receiving orthotopic heart and combined heart-lung transplants. This evolution has not been described previously. The evolvement is characterized in the early postoperative state by pulmonary hypertension with increased pulmonary vascular resistance. Right heart filling pressures are also quite high, and this may be required to maintain adequate left heart filling and forward cardiac output. Hemodynamics seem to normalize in most patients, with respect to resting right heart filling parameters, approximately 1 month after transplant. Indeed, by 3 months, the majority of our patients have normal resting mean, end-expiratory right atrial pressure. However, there is an occult restrictive myocardial abnormality that persists and can be demonstrated only by challenging the patients with volume. Interestingly, there are striking similarities in hemodynamic indices between isolated cardiac and combined heart-lung transplant patients, and importantly, tricuspid insufficiency (sometimes severe) is present.

There is no doubt that the orthotopically transplanted heart performs well enough to maintain patients at near normal functional level.[1,2] Still, this organ is not normal. Experiment demonstrates that transplanted hearts do not reinnervate their graft, respond to exercise differently, and require exogenous catecholamine stimulation to increase rate and contractility.[22,23]

The first reports of heart transplantation in humans gave only sketchy details regarding hemodynamics.[8-15,24] Still, it was noted that cardiac outputs were generally depressed in the early postoperative days and that high central venous pressures were essential.[8,10] An early report[11] summarized the hemodynamics in a single 46-year-old man 1 and 6 months after heart transplantation and demonstrated that the graft was denervated but responded to the stress of exercise and that the atrium actively contracted, contributing to active atrioventricular transport. One case series[13] described six human heart recipients and suggested that high right heart filling pressures were required early in the postoperative period to maintain an effective cardiac output.

Campeau et al.[14] reviewed five consecutive patients 4 to 20 weeks after transplantation. Within that follow-up window, it appeared most hemodynamic values at rest were within normal limits. However, when the data are scrutinized, resting pulmonary artery and right atrial pressures were mildly elevated and higher than in the control population. Interestingly, these authors[14] suggested that cardiac catheterization may actually aggravate or induce rejection and admonished it in patients with heart transplants. This may be one reason no detailed postoperative hemodynamic data are available from the early heart transplant experience.

The initial report[15] reviewing posttransplant hemodynamics during long-term follow-up evaluated eight patients at rest and during exercise 1 and 2 years after surgery and noted that resting intracardiac pressures were generally normal, but ventricular diastolic pressure rose dramatically during exertion. It was speculated that this might be a result of residual myocardial damage previously related to rejection or operation, or that this simply reflected the intrinsic pumping characteristics of a denervated preparation.

In patients undergoing combined heart-lung transplantation, only long-term follow-up data are, again, available,[25] since right heart catheterization is apparently avoided in the early postoperative period.[26] At 1 year, these survivors reportedly have normal resting pulmonary artery pressure, pulmonary vascular resistance, and cardiac output, but elevated blood pressure and systemic resistance. No right atrial or right ventricular pressure data are available; volume loading and exercise hemodynamics have not been performed.[25]

There are many plausible explanations for the diastolic abnormalities that we characterize. Analyses[27] of postmortem hearts from patients dying long-term after receiving cardiac allografts suggest that transplanted hearts may have left ventricular diastolic dysfunction caused by chronic ischemic heart disease. An analysis of chronic rejection has demonstrated that this problem may manifest primarily by obliterative proliferation in coronary arteries and is present in most allografts obtained from patients surviving at least 1 month or more. This finding is distinctly different from the findings of acute rejection, which are manifest by edema and myocardial cell swelling. Stinson et al.[15] hypothesized that interstitial fibrosis and coronary artery narrowing may be present as a result of chronic graft rejection and that these factors contributed to the sudden and rather dramatic elevation of left ventricular end-diastolic pressure during exercise. However, in this study, right ventricular function was not quantified, and interestingly, the rise in right ventricular end-diastolic pressure with exercise that is seen with volume loading was not demonstrated. Therefore the speculation may be incorrect, since we see evidence of diastolic dysfunction very early in the postoperative period.

We believe that the same disease processes occur in both ventricles and account for left ventricular diastolic dysfunction as well. As we report herein, this right ventricular dysfunction occurs early, and therefore it seems unlikely that this is the result of focal ischemia caused by atherosclerosis. Indeed, the fact that this abnormality diminishes with time but remains in occult fashion suggests a disease different from chronic ischemic heart disease. However, it is possible that operative ischemic time causes significant muscle derangement that accounts for abnormal hemodynamics.

In contradistinction to diastolic abnormalities that have been noted, systolic left ventricular function does not seem significantly altered or impaired in the transplanted heart in the absence of severe acute rejection. A recent study[16] demonstrated that 1 year after transplant, load-independent end-systolic indices of left ventricular contractility were normal. The conclusions were that the transplanted chronically denervated left ventricle had normal contractility and contractile reserve. This study also confirmed the fact that resting hemodynamics were generally normal but that left ventricular mass and end-diastolic wall thickness were greater for the transplant patients than for the control subjects. Others have made the same observation,[4] and we report similar findings herein.

It does not appear that the addition of cyclosporine to the immunosuppressive therapy of a heart transplant recipient alters, in itself, resting hemodynamics during long-term follow-up. Greenberg et al.[17] evaluated 19 patients 13 months after transplantation and demonstrated that only moderately abnormal hemodynamics were seen 1 year after this procedure. When a subset of patients had catheterization 2 years after transplant, many of these abnormalities had disappeared. The most frequent finding in their study was hypertension (56%), elevated left ventricular end-diastolic pressure (33%), and a reduced ejection fraction (28%). Biopsy review showed no relationship between fibrosis or inflammation and hemodynamic parameters, and these authors[17] concluded that mild to moderate hemodynamic abnormalities are common in the asymptomatic transplant patients receiving cyclosporine and prednisone. However, they suggest the possibility that myocardial fibrosis may cause hemodynamic abnormalities and that this fibrosis may be related to cyclosporine therapy.[7] These authors did not attempt to uncover occult restrictive hemodynamic patterns because they did not volume challenge the patients or report respiratory hemodynamic observations. Also, no attempt was made to characterize the evolution of hemodynamic indices over time.

One interesting recent report[28] evaluates six consecutive orthotopic transplant patients 1 year after surgery after infusing 1 L of normal saline solution over 8 minutes. The abnormal hemodynamic response that was uncovered resembles our observation. After volume, these patients' mean right atrial pressure increased at rest, paradoxically rose with inspiration, and revealed prominent X and Y descents. The authors[28] suggest that the source of diastolic restriction was myocardial and not pericardial in origin and implicated interstitial myocardial fibrosis as a cause of abnormal compliance, again speculating on an association between interstitial myocardial fibrosis and cyclosporine immune suppression.

None of the hemodynamic studies specifically compared biopsy or echocardiographic findings with hemo-

dynamic parameters. Our studies indicate that, at least early in the postoperative period, myocardial fibrosis is not significant and should not be invoked to account for compliance abnormalities. Likewise, in our population, diastolic dysfunction was apparent whether or not significant rejection was present. Additionally, because we prospectively followed our patients, we can demonstrate that right heart filling dynamics are abnormal at an early period. It is interesting that right heart filling pressures tend to decrease as the mean pulmonary artery pressure and pulmonary vascular resistance decreases. Also of interest is that the majority of patients have at least a small amount of tricuspid insufficiency after surgery. Indeed, two patients had a significant quantity, and these individuals had the most dramatic abnormalities in the right heart and were the most ill before the procedure.

The hemodynamic findings that we have characterized most resemble those dynamics associated with primary myocardial restrictive disease. Indeed, as Figures 2 and 4 demonstrate, our findings are most analogous to those described for elucidation of occult constrictive pericardial disease.[29] It is unlikely that restrictive pericardial disease is present this early, and therefore myocardial disease must be implicated. Still, it may be that a combination of factors contribute to the development of these hemodynamics. These processes might include a stunned or ischemic myocardium, infiltrative changes caused by rejection, small pericardial effusions that are common in the early postoperative period, atrial misshaping resulting from the implantation procedure, mild pulmonary hypertension, and volume overload. It seems likely that all of these are interrelated and that the hemodynamic findings are a composite that evolves over time so that right heart filling dynamics and pressure decrease as the pulmonary hypertension resolves and the heart recovers from its early postoperative state.

However, the most interesting observation is still the late, occult, myocardial restrictive pattern that must reflect intrinsic myocardial damage that persists in irreparable fashion. Of additional importance is that often the same process of evolution is seen with combined heart-lung transplantation, suggesting that the abnormalities are primarily myocardial and not influenced in other than an unmasking sense by pulmonary hemodynamics.

It is important to remember that high filling pressures seem normal in the early postoperative period and that during long-term follow-up, preload decreases. To completely characterize the hemodynamic abnormalities seen late after heart transplantation, volume loading is required.

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